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Bach, Silvia ; Richardson, Ulla ; Brandeis, Daniel ; Martin, Ernst ; Brem, Silvia

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Print-specific multimodal brain activation in kindergarten improves prediction of reading skills in second grade

Silvia Bach[1,2], Ulla Richardson[1], Daniel Brandeis[2,3,4], Ernst Martin[3,5], Silvia Brem[1,2,*]

Affiliations:

[1] *Agora Center, University of Jyväskylä, PO Box 35, 40014 University of Jyväskylä, Finland*

[2] *Department of Child and Adolescent Psychiatry, University of Zurich, Neumünsterallee 9, 8032 Zurich, Switzerland*

[3] *Center for Integrative Human Physiology, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland*

[4] *Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, 68159 Mannheim, Germany*

[5] *MR-Center, University Children's Hospital, Steinwiesstrasse 75, 8032 Zurich, Switzerland*

Corresponding author:

*Dr. Silvia Brem
Department of Child and Adolescent Psychiatry,
Neumünsterallee 9,
8032 Zürich, Switzerland
Phone: +41 43 499 27 60
Fax: +41 43 499 26 04
E-mail: sbrem@kjpd.uzh.ch

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Children who are poor readers usually experience troublesome school careers and consequently often suffer from secondary emotional and behavioural problems. Early identification and prediction of later reading problems thus is critical in order to start targeted interventions for those children with an elevated risk for emerging reading problems. In this study, behavioural precursors of reading were assessed in nineteen (aged 6.4±0.3 years) non-reading kindergarteners before training letter-speech sound associations with a computerized game (Graphogame) for eight weeks. The training aimed to introduce the basic principles of letter-speech sound correspondences and to initialize the sensitization of specific brain areas to print. Event-related potentials (ERP) and functional magnetic resonance imaging (fMRI) data were recorded during an explicit word/symbol processing task after the training. Reading skills were assessed two years later in second grade. The focus of this study was on clarifying whether electrophysiological and fMRI data of kindergarten children significantly improve prediction of future reading skills in 2nd grade over behavioural data alone. Based on evidence from previous studies demonstrating the importance of initial print sensitivity in the left occipito-temporal visual word form system (VWFS) for learning to read, the first pronounced difference in processing words compared to symbols in the ERP, an occipito-temporal negativity (N1: 188-281ms) along with the corresponding functional activation in the left occipito-temporal VWFS were defined as potential predictors. ERP and fMRI data in kindergarteners significantly improved the prediction of reading skills in 2nd grade over behavioural data alone. Together with the behavioural measures they explained up to 88% of the variance. An additional discriminant analysis revealed a remarkably high accuracy in classifying normal (n=11) and poor readers (n=6). Due to the key limitation of the study, i.e. the small group sizes, the results of our prediction analyses should be interpreted with caution and regarded as preliminary despite crossvalidation. Nevertheless our results indicate the potential of combining neuroimaging and behavioural measures to improve prediction at an early stage, when literacy skills are acquired and interventions are most beneficial.

Keywords: children, ERP, fMRI, prediction, reading

Introduction

Poor reading not only contributes to troublesome school careers but is often accompanied by secondary emotional and behavioural problems (Arnold et al., 2005, Mugnaini et al., 2009).

A major goal is thus to predict poor reading as early as possible and to start targeted intervention programmes to prevent severe reading and associated problems. Among children, poor readers include the 4-10% suffering from developmental dyslexia, a severe developmental reading disorder (Klicpera et al., 2007; Schulte-Körne et al., 1998).

Several studies have reported on the prediction of later reading skills by means of behavioural data collected before school. Apart from the familial risk, e.g. socio-economic status (Catts et al., 2001) and behavioural measures collected at preschool age, such as letter identification, phonological awareness (Schneider, 1993; Wagner and Torgesen, 1987; Wagner et al., 1997) and rapid naming tasks (Manis et al., 2000; Puolakanaho et al., 2007; Savage and Frederickson, 2005; Wolff et al., 1990) have been shown to provide good estimates for reading outcome, with accurate classification rates of e.g. 75% (Pennington and Lefly, 2001) or even 93% (Catts et al., 2001). When socioeconomic status and vocabulary development were controlled for, phonological awareness assessed during kindergarten significantly predicted word identification and spelling skills eleven years later (MacDonald and Cornwall, 1995). Rapid naming has been reported to be an important predictor of both reading accuracy and reading speed (Furnes and Samuelsson, 2009; Georgiou et al., 2008). In a recent study, rapid naming has been found to be a more robust long-term predictor compared to phonological awareness (Furnes and Samuelsson, 2010), a measure which has been reported to lose its predictive influence on reading difficulties after the early grades and, rather, predicts individual variation in early phases (Leppänen et al., 2006; Wimmer et al., 1991). Low letter knowledge before school has often been observed in children with severe problems in learning grapheme-phoneme associations and has thus also been proposed as a valuable predictor of an increased risk of developing a reading disorder (Lyytinen et al., 2004).

Despite rapidly growing knowledge about structural (Raschle et al., 2010) and functional differences in brain networks (Guttorm et al., 2010; Guttorm et al., 2005; Guttorm et al., 2003; Maurer et al., 2003; Specht et al., 2009; Benasich et al., 2006) even before learning to read, few studies have combined direct (electroencephalography: EEG) or indirect (functional magnetic resonance imaging: fMRI) measures of neuronal activation, and/or characteristics of brain structure with behavioural measures to improve the prediction of reading outcome. Electrophysiological measures with predictive value so far have mainly related to the processing of speech sounds. The lateralization of a late (540-630ms) positive auditory ERP discriminated newborns with and without familial dyslexia risk status (Guttorm et al., 2010; Guttorm et al., 2005; Guttorm et al., 2001; Guttorm et al., 2003). Furthermore, auditory evoked potentials of newborns discriminated the reading outcome at age 8 with 81% accuracy (Molfese, 2000). Finally the lateralization of the mismatch negativity (MMN) to speech stimuli in kindergarteners improved prediction of long-term reading outcome over behavioural data alone (Maurer et al., 2009) and correctly classified 81% of children at risk for dyslexia.

Beyond this, differences in brain structure or function measured with MRI may also improve the prognosis of long-term reading outcome: a priori defined morphometric measures of temporal and frontal areas in children between 6 and 16 years were able to classify dyslexics with 60% accuracy. By including behavioural measures such as age and IQ, the classification rate increased to 87% (Semrud-Clikeman et al., 1996). Hoeft and colleagues also showed that the combination of behavioural scores, grey and white matter morphological measures and functional activation explained 81% of the variance in the decoding ability, significantly more than behavioural data alone in children between 8 and 12 years (Hoeft et al., 2007). The latest work of the same group furthermore demonstrated that brain measures such as the activity in the right prefrontal cortex together with the white-matter organization of the right superior longitudinal fasciculus rather than behavioural measures alone, significantly predicted reading gains of dyslexics (Hoeft et al., 2011) thereby clearly demonstrating the potential of brain measures for neuroprognosis.

Other recently published studies have also pointed to functional activation and structural measures that are promising for prediction. An fMRI study by Specht and colleagues (Specht et al. 2009) revealed a negative correlation of the strength of activation in the occipito-temporal cortex and the dyslexia risk index and a structural MRI study reported significantly reduced grey matter volume in the left occipito-temporal and bilateral parieto-temporal cortex, the left fusiform gyrus and the right lingual gyrus in familial at-risk children in preschool (Raschle et al., 2011). Interestingly, most areas with diminished grey matter volume in at-risk children, and especially the basal left occipito-temporal cortex often referred to as the visual word form system (VWFS) (Cohen et al., 2000; Vinckier et al., 2007), plays a key role in print processing when children learn to read (Brem et al., 2010; Maurer et al., 2006). Several neuroimaging studies have revealed hypoactivation in posterior left-hemispheric regions in dyslexics (Kronbichler et al., 2006; McCrory et al., 2005; Shaywitz et al., 2002), and diminished functional activation of the VWFS in response to print has often been associated with poor reading skills across different languages (Paulesu et al., 2001; Shaywitz and Shaywitz, 2005) and different writing systems (Hu et al., 2010). The corresponding N1 (~170ms) ERP attenuation and its magneto-encephalographic homologue also point to diminished sensitivity to print in dyslexics (Helenius et al., 1999; Kronbichler et al., 2006; Maurer et al., 2007; van der Mark et al., 2009). Furthermore, the following evidence points to the potential of occipito-temporal activity for predicting reading skills at a young age: i) structural alterations within the VWFS of at-risk children before school enrolment (Raschle et al., 2011); ii) its importance in learning to read supported by the early and rapidly emerging sensitivity to letters or letter strings (Brem et al., 2010; Cantlon et al., 2011); iii) the neurophysiological differences between normal readers and dyslexics seen in the corresponding N1 ERP (Maurer et al., 2007). Because interventions for poor readers might be most beneficial when started in parallel with reading acquisition (Bradley and Bryant, 1983) the identification of predictors at preschool age would be particularly valuable. In this study, kindergarteners trained with a computerized grapheme-phoneme association game called Graphogame (Lyytinen et al., 2009; Lyytinen et al., 2007; Saine et al., 2011) which initiates and sensitizes specific brain areas to print processing (Brem et al., 2010). After about eight weeks of grapheme-phoneme training, the emerging neural correlates of print processing were examined with ERP and fMRI in the non-reading children by using an explicit word processing task with strings of symbols serving as the control condition. We then for the first time combined behavioural, electrophysiological and functional MRI measures at preschool age to examine whether the prediction of future reading skills could be improved.

Materials and methods

Study design and subjects

Forty native (Swiss-)German speaking kindergartners (mean age 6.4±0.3 years, 20 girls, 4 left-handed) took part in a larger longitudinal cross-over training study (also described elsewhere Brem et al., 2010) with two different non-commercial child-friendly, computerized training games (the “Graphogame” teaching grapheme-phoneme correspondences (Lyytinen et al., 2009; Lyytinen et al., 2007; Saine et al., 2011) and the control game teaching numbers and calculations (Räsänen et al., 2009)), behavioural and/or imaging sessions at kindergarten age and a behavioural follow-up in 2nd grade. Nineteen of these children (mean age 6.4±0.3 years, 14 girls, all right-handed) were selected for the current analyses because they had completed both an EEG and an fMRI session including an explicit word/symbol processing task after 8 weeks of grapheme-phoneme training (Lyytinen et al., 2009; Lyytinen et al., 2007; Saine et al., 2011) with appropriate data quality and task performance. Depending on children’s assignment in the longitudinal cross-over training study, after the initial behavioural assessment the children had started either with a period of grapheme-phoneme or a control training for proper balancing of the cross-over training study (for details about the training procedure see (Brem et al., 2010)).This design allowed us to assess all children after a highly consistent and well-defined literacy training phase focusing on grapheme-phoneme correspondence rather than reading. Children playing with the

Graphogame first (8 children) performed the EEG/fMRI i.e. approximately 108.0±78.3 days after the behavioural assessment (mean age 6.6±0.3 years). When playing the control number game first (11 children) the relevant EEG/fMRI session took place after the second training interval, i.e. 125.0±16.1 days after the behavioural assessment (mean age 6.7±0.3 years). The separate EEG and fMRI recordings after the Graphogame training took place within 4.0±3.0 days (order of EEG, fMRI recordings counterbalanced: eight of the 19 children started with the EEG). At the time of the longitudinal behavioural follow up in 2nd grade the children were 8.4±0.3 years old. Note, all children also performed an audiovisual implicit word and falsefont processing task in the imaging sessions before and after the training periods as described elsewhere (Brem et al., 2010).

At kindergarten a behavioural test battery was conducted with all children prior to the start of the trainings. In addition, the parents rated their children's behaviour by the Child Behaviour Checklist (CBCL) (Achenbach, 1991) and retrospectively estimated their own reading and writing competencies in school (adult reading history questionnaire, ARHQ) (Lefly and Pennington, 2000). Screening with the CBCL (Achenbach, 1991) attention score showed that all children had attention scores below the clinical cut-off (≤67). Based on the parents' ARHQ mean score (≥ 0.4) 3 of the 19 children were classified to have a "familial risk" for dyslexia (at-risk). And one of these "at-risk" children was classified as a poor reader two years later. The years of parental education served as an estimate of children's socioeconomic background (SES) (Brem et al., 2010). Further we rated the literacy environment based on the number of books of the parents and the children themselves.

The behavioural assessment was accomplished at children's home, where also the imaging procedures were explained to the children with pictures. Behavioural measures assessed in all kindergarteners before starting the trainings ("pre-training") were IQ (CPM: Coloured Progressive Matrices, children with an IQ ≥80 were included in the study) (Raven, 2002), receptive vocabulary and word comprehension (two subtests of the "Marburger Sprachverständnistest für Kinder, MSVT") (Elben and Lohaus, 2000), rapid naming of objects (RAN), letter knowledge (LK: including upper and lower case letters whereby letter sound and letter name were considered as correct responses), reading (tested with a word reading subtest of the "Salzburger Lesetest, SLT") (Landerl et al., 1997) and precursors of reading and writing skills as implemented in the BISC screening test battery ("Bielefelder Screening zur Früherkennung von Lese-Rechtschreibschwierigkeiten, BISC": a screening test battery for the early detection of children with an elevated risk to develop reading and writing difficulties at school age. This test battery allows to determine a risk score ("BISC risk") at kindergarten age. The BISC risk score is a composite score computed by the performance in several subtests such as pseudoword repetition, rhyming of word pairs, visual word comparison, phoneme association, colour naming, syllable segmentation, phoneme extraction (Jansen, 1999)). For further analysis we used the BISC risk point score (the "BISC risk score" can be computed by the performance of a child in all subtests and indicates whether a child has a high risk for developing reading and/or spelling difficulties) and two summary measures reflecting either phonological awareness in a broad sense (PAbs) or phonological awareness in a narrow sense (PAns). PAbs is linked to speech skills associated with rhyming and clapping games and is thus formed by the sum raw scores of the subtests rhyming of word pairs and syllable segmentation. The PAns is considering the analysis of the phoneme structure without a rhythmic, segmental language context and is defined by the summed raw scores of the subtests phoneme association and phoneme extraction (Jansen, 1999). LK (upper and lower case) and reading skills were assessed before and after the Graphogame (in either the EEG or fMRI session). The gain in LK was determined as the difference between post- and pre-training LK. Before training and also after the grapheme-phoneme training period (n=19: average training time: 321.5±124.3 minutes; average training period: 54.4±8.5 days) children were "non-readers", i.e. no child was able to read more than 6 out of 30 words (high-frequency nouns of a German word reading test, the SLT (Landerl et al., 1997)) when given as much time as needed except for only two children who showed very rudimental reading skills after training as they were able to decode 8 or 17 out of 30 words. Note, formal reading instruction in Switzerland starts in first grade, i.e. at the age of 7 years.

Analogous to our previous study (Bach et al., 2010) children scoring above the 40th percentile in the standardized reading test in 2nd grade (number of correctly read words per minute, subtest of SLT (Landerl et al., 1997)) were considered as normal readers (NR=11), children scoring below the 25th percentile as poor readers (PR=6) (Bach et al., 2010; Manis et al., 1996; Shaywitz et al., 2003). The children scoring between the 25th and the 40th percentile were assigned to the gap group (GG=2) and excluded for all group comparison analyses.

Task

Besides an audiovisual modality judgment task described elsewhere (Brem et al., 2010) children performed an explicit word/symbol processing task. The explicit word/symbol processing task was only conducted in the imaging session after the grapheme-phoneme training period (Fig. 1). Children were instructed to try to decode the presented words (W) and to decide by the left/right button press of their left/right index finger whether it referred to an animal or not. In general, despite the relatively long presentation time children were not able to read the short, high-frequency nouns but they tried to decode (guess). In the control condition the children solved a visual symbol (S) discrimination task and indicated by button press whether strings of hash signs (#) contained an asterisk (##*#) or not (####).

The assignment of response buttons was counterbalanced across the children but kept constant for the EEG and fMRI measurements (9 of 19 children pressed left for an animal word). Words and symbols in black were presented in the middle of a white screen for 5250ms while static pictures of a dog/crossed out dog and strings of hash signs with/without asterisk (to remind the children which button to press) were always visible on the screen, also during the ISI of 500ms in which a fixation cross was shown. The two conditions were presented pseudo-randomly. The EEG task consisted of two parts (task duration 2x6.33 minutes) in order to have enough stimuli (40 stimuli/condition) to compute ERPs. In addition, 26 null events were pseudorandomly interspersed. Children were allowed to take a short break in between the parts. The event-related design of the fMRI task included 20 stimuli/condition and 36 null events pseudorandomly interspersed (task duration 7.28

minutes). To verify that only children who attended and responded to the stimuli were included in the analyses, a minimum overall accuracy of 65% correct responses to symbols served as inclusion criteria (for subject inclusion criteria, omissions were counted as incorrect responses). No specific performance criteria were set for words as children were not able to read. The analyses on accuracy in task performance concentrated on those trials for which a behavioural response was given only, but also the rate of omissions is reported. Multivariate analyses of variance (MANOVA) were calculated separately for task performance (accuracy, omissions) in the EEG and fMRI sessions (factors condition and group).

EEG Recording and processing

The children sat in front of a computer screen (distance 120cm). The ERPs were recorded from 64 channels at 500Hz (recording reference Fz recomputed offline to average reference, ground: AFz, filters 0.1-70Hz, impedances below 15kOhm). Post-processing included down-sampling to 256Hz, filtering 0.1-30Hz, artefact rejection (100µV; for two children 125 µV) and correction of eye movements using ICA (Jung et al., 2000). A minimum of 15 epochs per condition (mean W: 29.7±6.4; S: 30.1±6.5) was required for computing condition averages. The EEG was recorded using caps which included all 10-20 system electrodes as well as supplemental electrodes FPz, FCz, CPz, POz, Oz, Iz, AF1/2, F5/6, FC1/2, FC3/4, FC5/6, FT7/8, FT9/10, C1/2, C5/6, CP1/2, CP3/4, CP5/6, P5/6, TP7/8, TP9/10, PO1/2, PO9/10, OI1/2, PPO9h/10h and two EOG electrodes below the outher cantus of each eye. To provide a better coverage O1′/2′ and Fp1′/2′ were placed 15% more laterally to Oz/Fpz. At the midline in between Oz and Iz, OI1 and OI2 were placed to more evenly cover the occipital scalp.

The data was epoched (-100ms to 1500ms after the stimulus) and transformed to the average reference (Lehmann and Skrandies, 1980) before computing separate averages for words and symbols. The N1 interval was defined as the interval between two subsequent global field power (GFP) sinks (188-281ms) in the grand mean waveform for words and symbols. As in our previous studies (Brem et al., 2010; Maurer et al., 2006) the mean amplitude of the N1 interval within a left occipito-temporal electrode cluster (LOT: O1’, P7, PPO9h, PO9) was determined for each condition and the condition difference (W-S). These mean values in the N1 at LOT were subjected to a condition by group MANOVA. To examine whether the N1 at LOT was correlated with phonological measures (BISC risk point score, PAbs, PAns), language related skills (receptive vocabulary, word comprehension, RAN, LK and LK gain measures) or training time correlations were computed. Further the N1 was used as a predictor in regression and discriminant analyses.

fMRI Recording and processing

The fMRI data was acquired on a 3-T scanner (GE Medical Systems) using an echo planar imaging sequence (25 axial slices covering the whole brain, TR 1500 ms, TE 31ms, matrix 64x64, voxel size 3.75x3.75x5mm, slice thickness/gap 4.6/0.4 mm, flip angle 50°, FOV 240 mm^2). The children were stabilized using custom-made padding and fixations. Earplugs, headphones and a noise insulation mat protected the child from scanner noise. Visual stimulation was presented with MR compatible (TFT) video goggles. During the task responses were collected by a response box. The children were accustomed to the scanner by a demonstration of the scanning procedure with a teddy bear.

SPM5 (Wellcome Department of Cognitive Neurology, London, http://www.fil.ucl.ac.uk/spm) was used for processing and analysis. The first 4 scans were always excluded to avoid T1 saturation effects, images were slice-time corrected, realigned and normalized (7th-degree spline interpolation) to match the Montreal Neurological Institute template (MNI), resampled ($3mm^3$ voxels) and smoothed with a 9mm FWHM isotropic Gaussian kernel. Based on the SPM realignment procedure, we included only those children for whom more than 97.5% of the total 295 scans did not exceed the threshold of maximum 2.5mm/2.5° translation/rotation displacement during task completion in the x, y or z plane. The few scans exceeding the translation/rotation threshold were substituted by neighbouring scans. The event-related activation of both conditions was modelled using the standard SPM hemodynamic response function and filtered with a 128-s high-pass filter. The second-level random effect analyses were based on the individual contrast images. The threshold (p<0.005, k≥29) reported in our study is corrected for multiple comparisons by using a cluster extent threshold criterion determined by the Monte Carlo simulations procedure (in MATLAB, 10000 simulations) to enforce an a priori corrected threshold of $p<0.05$ (Slotnick et al., 2003; Slotnick and Schacter, 2004). The Talairach Daemon (Lancaster et al., 2000) was used to identify brain structures after transformation of the MNI coordinates into Talairach coordinates (by the mni2tal formula (http://eeg.sourceforge.net/doc_m2html/bioelectromagnetism/mni2tal.html)).

Percent signal change from six spherical (radius=5mm) regions of interest (ROI) was extracted on unsmoothed images for W and S by using MARSBAR toolbox (version 0.41), provided by M. Brett (http://marsbar.sourceforge.net). The selection of the ROI in the VWFS was based on previous literature (MNI x, y, z:-42, -54, -17) (Brem et al., 2009; Cohen et al., 2000; van der Mark et al., 2009) whereas the centres of the other five ROIs corresponded to the regional maxima of the functional activation difference (W-S). To avoid circularity effects (Kriegeskorte et al., 2009; Vul et al., 2009) a MANOVA (factors condition and group) was performed for the literacy based VWFS ROI only.

The condition difference in the VWFS was further correlated with phonological measures (BISC risk point score, PAbs, PAns), language related skills (receptive vocabulary, word comprehension, RAN and LK and LK gain measures) and training time.

Prediction analyses

Pearson correlations: To determine the variables to be included in the subsequent multiple regression analysis, one-sided Pearson's correlations were computed between each behavioural and demographic measure and the performance in the reading test in 2nd grade. These correlations are reported in table 1.

Multiple linear regression analysis

Forced entry method: The reading score (percentiles) of the 2nd graders was used as the criterion variable in our core multiple regression analysis. Only behavioural predictor variables showing significances in one-sided Pearson's correlations with the reading score in

2nd grade (Table 1) were used for this multiple regression analysis. To limit the number of variables again, we only used the summary measures for phonological processing (BISC risk point score, PAbs and PAns) instead of all significant single subtests and the total pre- and post-training LK (upper+lower case) or the total gain in LK.

For the multiple linear regression and the preliminary discriminant analyses we report both uncorrected and Bonferroni corrected *p*-values (accounting for the amount of selected predictor variables). Corrected values are marked with an asterisk (*) throughout the text and tables. Assumptions for regression analyses such as multicollinearity, homoscedasticity, independence and normal distribution of errors, tested by correlational matrices, Levene test and Durbin-Watson test, were met.

Hierarchical stepwise method: In addition to behavioural measures the N1 mean amplitude of the condition difference (W-S) between 188 and 281ms at LOT and the corresponding differential activity (W-S) of the VWFS ROI were used as neuroimaging predictors. To test whether N1 and VWFS measures significantly explained additional variance in the reading score in 2nd grade over behavioural measures alone, we used a stepwise procedure. Behavioural measures were entered as one block and the N1 and the VWFS activations were entered as separate blocks (adding $p<0.05$, keeping $p<0.10$ significant predictors).

Preliminary discriminant analyses

A preliminary discriminant analysis was conducted in order to classify future normal and poor readers (NR>40th percentile: n=11; PR<25th percentile: n=6). Given the limitations regarding validity and reliability of the performed discriminant analyses with the small sample sizes used here, the results of this analysis are referred to as preliminary and therefore need to be interpreted with caution. The predictor variables were entered using minimized Wilks' lambda at each step. Normal distribution (Kolmogorov-Smirnov test) and equality of covariance matrices between groups (Box's M test) was confirmed for all variables of interest. Only variables contributing to the discrimination (probability for predictors to enter set at $p<0.05$, to remove at $p>0.1$) were included in the stepwise analyses. The leave-one-out method was used for cross validation.

Results

Behavioural task performance

The MANOVAs for accuracy (computed only for trials with a behavioural response) with factors group (11 NR/5 PR, one PR excluded due to a very high rate of omissions in word trials) and condition (W/S) showed a significant main effect of condition (EEG: $F(1,14)=43.4$, $p<0.001$; fMRI: $F(1,14)=27.9$, $p<0.001$). This main effect demonstrated that performance in symbol discrimination was better than in word classification (EEG accuracy: W=76.5.2±14.6%; S=96.8±4.5%; EEG omissions: W=51.1±26.2%; S=8.3±6.3%; fMRI accuracy: W=61.2±18.0%; S=93.0±8.2%; fMRI omissions: W=40.0±30.4%; S=5.0±5.8%). There was also a main effect of group ($F(1,14)=13.0$, $p=0.003$) and an interaction of condition and group ($F(1,14)=6.5$, $p=0.023$) for the EEG performance. The performance in classifying words was thus better in future NR than PR while symbol discrimination accuracy was similarly high in both groups. The MANOVA for omissions with factors group and condition showed a condition main effect with more omissions to word stimuli (EEG: $F(1,15)=55.5$, $p<0.001$; fMRI: $F(1,15)=24.7$, $p=0.001$). The high rate of omissions indicated that children pressed too late or remained indecisive and did not respond whenever they felt insecure about the response. The excellent performance in symbol discrimination and the above chance level performance for word classification also showed, that the children were able to follow the task instructions.

EEG results

A more pronounced activity to words vs. symbols was found over the occipito-temporal cortex as visible in the t-maps and the t-curve at left occipito-temporal (LOT) sites in Figure 2. The MANOVA of the N1 mean value at LOT revealed a highly significant main effect of condition ($F(1,15)=9.9$, $p=0.007$) showing a more pronounced negativity to words than symbols. The condition difference at LOT correlated with RAN ($p=0.036$, $r=-0.423$), pre-training LK ($p=0.026$, $r=-0.454$; lower case $p=0.013$, $r=-0.510$) and post-training LK ($p=0.028$, $r=-0.446$; upper case $p=0.016$, $r=-0.494$).

fMRI results

The activation for words and symbols (Table 2, Fig. 3) comprised a bilateral network, mainly including occipital and frontal areas. The condition difference was dominated by activity in the left inferior frontal gyrus (IFG), the left and right medial frontal gyrus (MFG) as well as the left and right middle temporal gyrus (MTG) (Table 2). Print sensitive activity in the VWFS (fusiform gyrus) with more activity for W than S emerged at a slightly lower threshold ($p<0.005$, k=26) for the whole sample but reached a corrected significance level when looking at the kindergarten children with normal reading skills in 2nd grade (n=11) (Fig. 4). Note, no significant group difference in print specific activation was found in a whole brain analysis.

The MANOVA of the VWFS ROI showed a trend for a condition main effect ($F(1,15)=3.9$, $p=0.066$) with stronger activity for words. Further, VWFS activity correlated with the gain in letter knowledge of lower case letters after Graphogame training ($p=0.021$, $r=0.472$) and the BISC risk point score ($p=0.035$, $r=-0.424$).

Behavioural assessment data

Note, all correlation and prediction analyses that are based on behavioural assessment data in kindergarten and 2nd grade were also computed for a larger sample of 40 children and are reported in the supplementary information (SI) online (SI1).

The group comparisons as well as the correlation of each behavioural kindergarten measure with the 2nd grade reading score are summarized in Table 1. NR differed significantly from PR in RAN, receptive vocabulary, PAbs and pre-training lower case LK and tended to differ regarding the literacy environment of the child. The correlations with 2nd grade reading scores yielded significances for RAN, receptive vocabulary, PAbs, PAns, pre-training lower case LK, pre-training total LK and all post-training LK measures.

A reliable increase in LK due to training was found for letter knowledge as shown by the paired t-tests of pre- vs. post-training letter knowledge measures (all $p<0.001$) and the significant correlation of training time with letter knowledge (post-training upper case LK $p=0.042$, $r=0.471$) and letter knowledge gain (total LK gain $p=0.025$, $r=0.513$).

Multiple linear regression analysis

Based on significant Pearson's correlations, the following behavioural measures were used as predictors (simultaneous forced entry of 5 predictors: RAN, receptive vocabulary, PAbs, PAns, LK, see table 1). To minimize the total number of behavioural predictors we only entered one post-training LK (total) measure (but see SI2A for pre-training LK). Even though there was no significant correlation of letter knowledge gain (upper case, lower case or total letter knowledge gain) with reading score in 2nd grade we repeated this analysis and substituted post-training LK with the total gain in LK. The results of this subsidiary analysis corresponded to the core analysis (see SI2B).

Hierarchical stepwise method

The behavioural measures collected at kindergarten significantly predicted reading outcome in 2nd grade (R=.80, $F(5,13)=4.7$, $p=0.011$) and explained a considerable amount (adjusted R^2: 51%) of the variance. Importantly, when adding N1 print sensitivity, the explained variance increased significantly to 67% ($p=0.017$). The VWFS print sensitivity again significantly contributed to the prediction ($p=0.003$*) and increased the amount of explained variance to 84% (Table 3).

According to the standardized β-coefficients (Table 3) RAN ($p<0.001$*), the mean value of the N1 condition difference at LOT ($p=0.001$*) and the VWFS ($p=0.003$*) significantly contributed to the prediction in our model. Therefore they were chosen as predictor variables for a subsequent "preliminary" discriminant analysis to distinguish NR and PR.

Note, we repeated this analysis by substituting the VWFS ROI with each of the five functionally defined ROIs (see Table 2, W-S). Only the ROI in the left middle temporal gyrus significantly contributed to prediction: The left MTG print sensitivity together with the behavioural measures and the N1 explained 78% (p=0.027) of the variance (see also SI2C).

Preliminary discriminant analysis

The following preliminary discriminant analysis did not include the two children with intermediate reading scores in between the 25^{th} and the 40^{th} percentile. The stepwise procedure showed, that error variance was continuously and significantly diminished by including the following variables RAN, N1 and VWFS (RAN: p=0.034; RAN and N1: p=0.005*; RAN, N1 and VWFS: p=0.001*). Accordingly, these three variables significantly discriminated poor and normal reading 2^{nd} graders (Eigenvalue=2.23, canonical correlation=0.83, Wilks' Λ= 0.309, $\chi 2(4)$=15.84). The other variables PAbs, PAns and LK did not further contribute to classification. The leave-one-out cross-validation method yielded a correct classification of 94.1% (sensitivity: 100%; specificity: 90.9%). Additional analyses were performed by using a cut-off 40^{th} percentile criterion (see SI2D) for grouping the children. In this way also the children of the gap group remained in the analyses. These subsidiary analyses converged with the reported core analysis and achieved a similar classification accuracy.

When repeating the core discriminant analysis with the left MTG (instead of VWFS) (see SI2C), this variable did not significantly improve the classification achieved by RAN and N1 (Eigenvalue=1.16, canonical correlation=0.73, Wilks' Λ= 0.464, $\chi 2(4)$=10.75). The leave-one-out cross-validation method therefore yielded a slightly poorer classification of 82.4% (sensitivity: 100%; specificity: 72.7%).

Discussion

In this study we combined behavioural, electrophysiological and functional MR measures collected in kindergarten to predict future reading outcome in 2nd grade. In addition to standard behavioural literacy screening tests used in non-reading kindergarteners, neuroimaging measures were collected from the same children after an eight week grapheme-phoneme association training (Graphogame) (Lyytinen et al., 2009; Lyytinen et al., 2007). Even though the children were still not able to read after the rather short training period, their basic grapheme-phoneme correspondence knowledge improved and initiated activation in neural networks for reading as reported in Brem et al. 2010. The EEG and fMRI data were recorded during attempted explicit word reading/decoding vs. judging visual characteristics of symbol strings.

Prediction of reading outcome with behavioural measures

In accordance with previous studies aimed at predicting dyslexia with behavioural assessments (Catts et al., 2001; Lyytinen et al., 2009; Maurer et al., 2009; Puolakanaho et al., 2007) we replicated the predictive potential of specific behavioural measures at kindergarten age for later reading outcome. Phonological awareness (Liberman et al., 1974; Snowling, 2000), rapid naming (Compton, 2000; Compton et al., 2001; Manis et al., 2000) and letter knowledge (Pennington and Lefly, 2001; Puolakanaho et al., 2007) measured in kindergarteners correlated with reading in 2nd grade and together explained 51% of the variance. While RAN significantly improved classification of poor and normal reading 2nd graders, letter knowledge and phonological awareness did not contribute to this discrimination, even though letter knowledge has repeatedly been identified as an important indicator of later reading problems at preschool age (Pennington and Lefly, 2001; Puolakanaho et al., 2007), especially in consistent languages. One could reason that letter knowledge in previous studies was always assessed before specific literacy training (such as grapheme-phoneme training) thereby reflecting children's self-attained knowledge and thus serving as a more reliable predictor. But when using pre-training letter knowledge (SI2A) instead of post-training letter knowledge as predictor variable, a similar amount of variance was explained (54%). Only through substitution of post-training letter knowledge with the gain in letter knowledge through training, was a better prediction result achieved (59%, see SI2B). There is some evidence that phonological awareness is a poorer long-term predictor compared to rapid naming (Furnes and Samuelsson, 2009; Georgiou et al., 2008) but it seems to be important in early grades as also indicated by prediction analyses in our behavioural sample (see Table SI-1). Another important predictor of reading is the child's home literacy environment encompassing various factors such as for example shared reading, parental encouragement, library visits and others (Burgess et al., 2002; Whitehurst and Lonigan, 1998). Examination of home literacy environment on reading achievement was not a main aim of this study and therefore we only recorded the number of books at the children's home to roughly estimate their literacy environment. Because no significant correlation between the number of books (children or parents) and the reading performance in second grade was found we did not further evaluate its predictive potential for our imaging sample. For our larger behavioural sample (see SI) a trend for a correlation between the number of the child's books and its reading performance was detected but inclusion of this measure in the hierarchical stepwise regression analysis did not improve prediction. This result, may not question the importance of home literacy environment for children's reading achievements but rather indicates that literacy environment should not be measured using solely one variable (Burgess et al., 2002; Whitehurst and Lonigan, 1998).

Neural activation to print and symbol processing

In accordance with our previous article (Brem et al., 2010), non-reading kindergarteners showed sensitivity to print over symbols in the form of an occipito-temporal negativity in the N1 time range (188-281ms) after learning the principles of grapheme-phoneme associations (Brem et al., 2010; Maurer et al., 2006). Correlations of letter knowledge measures with this left occipito-temporal activation in the N1 at LOT support its role in the development of print specificity. In accordance with the ERP measures, the whole brain analysis of the fMRI data also yielded print sensitive activation in the VWFS. The more pronounced activation to words than symbols in the VWFS appeared at a slightly lower and uncorrected statistical threshold in the data of the whole group. For the eleven kindergarten children who achieved normal reading scores in 2nd grade, however, the differential activation in the VWFS survived the cluster-extent corrected threshold. The correlation of print sensitivity within the VWFS ROI, and the gain of lower case letter knowledge, underlined the important role of this region for emerging literacy.

Previous studies showed that print sensitivity is diminished in young dyslexic children (Maurer et al., 2007) but may normalise after they have gained experience with reading (Maurer et al., 2011) although dyslexic adults also show deficient sensitivity (Helenius et al., 1999; Shaywitz and Shaywitz, 2005). Together with the recent finding of clear functional and structural alterations in the left occipito-temporal cortex (Raschle et al., 2011; Specht et al., 2009) of preschool children with a familial risk of dyslexia, these studies thus clearly point to the potential power of print sensitivity as an index for successful reading acquisition.

In line with our expectation, the differential N1 mean amplitude at kindergarten age significantly contributed to both the prediction and classification of poor and normal readers in 2nd grade and together with behavioural measures explained 67% of the variance in our group. Moreover, and in accordance with the above, print sensitivity measured as percent signal change in the VWFS also significantly improved the explained variance in reading skills at 2nd grade by 17%. A total of 84% of the variance in the reading skills of 2nd graders could thus be explained by behavioural, ERP and fMRI measures collected at kindergarten age. A preliminary discriminant analysis corroborated this result by yielding high sensitivity and specificity when using the same behavioural, ERP and fMRI measures in kindergarten to differentiate between future normal and poor reading children.

As a more explorative approach we also investigated (see SI2C) whether any area that exhibited significantly more pronounced activity to words than symbols in the whole brain analysis of kindergarteners would explain further variance. These areas largely belonged to the characteristic language network and included areas in the left and right frontal and temporal lobes. Only the area in the left middle temporal gyrus contributed to the prediction of future reading skills by explaining 78% of the variance in later reading skills (see SI2C) together with the behavioural and ERP measures. The activity in the middle temporal gyri has been related to phonological processing and more specifically may directly reflect grapheme-phoneme decoding, a process that is affected in poor reading children (Jobard et al., 2003; Rumsey et al., 1997; Sakurai et al., 2000). However, middle temporal areas have also been implicated in accessing lexical and semantic information in terms of a sound-to-meaning interface network (Hickok and Poeppel, 2000, 2004, 2007). In their meta-analysis Vigneau and collaborators (Vigneau et al., 2006) have attributed a role in semantic processing and verbal knowledge to the left middle temporal area. Even though our children were still not able to read and classify the words, as confirmed by the high rate of omissions, it is highly likely that they were searching for a meaning: When the children pressed a button, their response was well above chance. It seems that the children tried to decode the words but often remained indecisive, answered too late and responded only, when they were quite sure about the meaning of the word. Therefore it seems reasonable to assume that some children were able to identify a few words. The contribution of the left middle temporal gyrus in the prognosis of reading outcome may reflect the development of a sound-to-meaning interface.

The activation in the left inferior frontal gyrus has repeatedly been associated with phonological processes as shown by the meta-analysis of Vigneau (Vigneau et al., 2006) or a series of studies using either auditory (Booth et al., 2007; Cao et al., 2006; Ruff et al., 2008) or visual tasks (Bach et al., 2010; Bitan et al., 2006; Poldrack et al., 1999). Its pronounced activation is in line with the well established view that phonological processes are especially important at the beginning of reading acquisition (Coltheart et al., 2001; Ehri, 1998). Finally, the activation in the medial frontal gyrus could reflect the automatic allocation of attention to words (Peng et al., 2003). Whether activation in these areas might contribute to the prediction of reading later in development needs to be clarified by future studies.

Interestingly, the frontal and temporal areas exhibiting more pronounced activation to words in our explicit word processing task did not show differential activity when an implicit task was used (Brem et al., 2010), which is in contrast with adult readers or normal reading school children who also show this differentiation during implicit word processing (Brem et al., 2009; Price et al., 1996; Vinckier et al., 2007). This might indicate on the one hand that children at least tried to read after receiving the explicit instruction, but more likely suggests that only specific stages of word processing are automatized at this early phase of reading acquisition. Viewed the other way round, the implicit print processing task highlighted the emerging print sensitivity in the occipito-temporal cortex acquired when learning grapheme-phoneme correspondences, in line with the letter-specific response reported for 4-6 year-old non-reading children in a recently published study (Cantlon et al., 2011) investigating category-specific cortical representations in young children.

Limitations of the present study

In this study we aimed to follow a homogenous sample of healthy young children within a narrowly defined educational age range, and with strict criteria regarding confounding factors such as their native language. The very young age of the participating children, the application of different imaging techniques within the same children and the longitudinal design of the study resulted in a relatively small but well defined sample (n=19) for combined behavioural, EEG/fMRI prediction analyses. We acknowledge that the small sample size in this study has important implications for the validity and reliability of the statistical analyses and their interpretation. The use of small sample sizes may result in overfitting the data and overstressing a characteristic of a specific group. Such models thus may fail to provide valid predictions in a sample other than the one used to specify the model. Therefore, the high sensitivity and specificity found in the discrimination analyses as well as the regression analyses should be interpreted with caution and regarded as preliminary results despite crossvalidation. Nevertheless, the results in this particularly valuable sample are important and correspond nicely to the hypothesis based on previous studies that print sensitivity can contribute to the prognosis of reading outcome at an early age. Our preliminary analyses thus show the potential of specific imaging measures in predicting early reading outcome, i.e. before children learn to read at school. Predictions about future reading skills with neuroimaging measures have already been demonstrated for preschool (Raschle et al., 2011; Specht et al. 2009) and older children by using structural and functional MR measures (Hoeft et al., 2011; Hoeft et al., 2007) or for very young children based on ERP data on auditory processing (Guttorm et al., 2010; Guttorm et al., 2005; Maurer et al., 2009; Molfese, 2000; Benasich et al., 2006). Our data are thus in line with a series of recent articles that demonstrate the potential of neuroimaging measures to improve prediction. Given the limited group sizes in this study, replication studies with larger samples are certainly needed to corroborate the present results.

To address the problem of the small samples in the discriminant analysis, the analysis was repeated (see SI2B) after inclusion of the two children with “intermediate” (between the 25th and the 40th percentile) reading skills, and a similar classification of “better” (>40th percentile) and “poorer” (<40th percentile) readers was achieved.

Another limitation is the selection of an explicit word processing task in children who were not able to read as confirmed by the high rate of omissions for word stimuli. In contrast to our implicit paradigm described elsewhere (Brem et al., 2010), our intention here was not only to retain children’s attention on the stimuli but also to stimulate in-depth letter string processing to examine precursor processes of reading such as letter decoding. The condition difference in the ERP, and the differential fMRI activation within the well known reading network substantiated that this aim was achieved.

Conclusion

No study to date has combined neuronal activity measures acquired with different imaging techniques and behavioural measures to improve the prognosis of later reading skills. Because ERP and fMRI are sensitive to different aspects of information processing their combination might critically advance prediction of reading skills as demonstrated in the present article. In our sample of nineteen children, the print sensitivity of the N1 and the VWFS together with behavioural data in kindergarten achieved a remarkably accurate prediction of reading skills in the same children two years later. Even though the present results need to be confirmed by future studies with larger sample sizes, our preliminary results provide evidence for the enormous potential of combining functional markers from different imaging techniques for pre-dating reading outcome at preschool age. Certainly, the approach in our study is time-consuming and expensive, but its application could yield a tool that more precisely predicts future reading outcome (competence) at preschool age. Particularly children with an elevated familial risk for future reading problems could be screened before school, and if required, receive targeted therapy before reading problems and negative school experiences emerge.

Supplementary material

Supplementary material (SI) is available at Neuroimage online.

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Figure legends

Figure 1: Task procedure: short words (W) and symbol strings (S) were pseudorandomly presented to the children. The children decided whether the symbol strings contained an asterisk (*) (right button press) or not (left button press) and tried to decide whether the word denoted an animal (left button press) or not (right button press).

Figure 2: (Upper) Event related-potentials at left occipito-temporal sites (LOT: mean of O1', P7, PPO9h, PO9) are illustrated: words (red), symbols (blue), the condition difference (green) and the t-values of the condition difference (orange). Bars on the right depict the mean N1 amplitudes of words and symbols (averaged values: 188-281ms) (p<0.01**). (Lower) Potential field maps of the mean N1 amplitude to W (red), symbols (blue), their difference (green) and t-maps (orange) of the N1 interval (188-281ms).

Figure 3: (Upper) Brain activity elicited by (p<0.005, k≥29, t≥2.88) (A) word > rest, (B) symbol > rest and (C) the difference of words vs. symbols. The corresponding activations are listed in Table 2. Horizontal sections on the right display the activation (thresholded from t=2.5 to t=7) in the VWFS. The bars below illustrate the percent signal change in the VWFS ROI for words and symbols ((*)=trend).

Figure 4: Brain activity elicited by the difference of words vs. symbols in the group of future normal reading children (n=11, p<0.005, k≥29, t≥3.17). Horizontal sections on the right display the activation (thresholded from t=2.5 to t=7) in the VWFS.

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Table 1: Group comparison for demographics and behavioural tests (imaging group).

	Groups according to reading scores in 2nd grade			n=19
Behavioural measures in kindergarten	**NR (n=11) (>40Percentile)** Mean ± SD	**PR (n=6) (<25Percentile)** Mean ± SD	***P (groups)***	***P one-sided Pearson's correlation with reading score in 2nd grade***
Reading score in 2nd grade (words per minute score **SLT**; percentile)	68.92±17.87	14.20±6.92	***<0.001***	
Pretest age (years at behavioural assessment at home)	6.35±0.29	6.33±0.19	*0.923*	*0.389*
Attention score (**CBCL**)	48.09±8.58	45.63±6.78	*0.555*	*0.314*
IQ (Raven) (ss)	56.77±9.19	56.00±6.14	*0.857*	*0.413*
ARHQ (mean)	0.26±0.10	0.29±0.11	*0.606*	*0.148*
Training time (minutes)	333.88±130.15	300.43±136.23	*0.625*	*0.254*
Rapid naming **RAN** (speed in seconds)	39.64±7.93	48.17±5.49	***0.034***	***0.008***
Receptive vocabulary (**MSVT**) (ss)	57.27±5.00	48.33±4.46	***0.002***	***<0.001****
Word comprehension (**MSVT**) (ss)	48.73±8.05	49.67±7.53	*0.817*	*0.639*
BISC risk score	1.45±1.69	2.17±1.17	*0.377*	*0.224*
Phonological awareness (broad sense) **PAbs**	17.82±1.94	14.17±2.93	***0.007***	***0.011***

Phonological awareness (narrow sense) **PAns**	19.18±1.08	17.50±2.26	*0.134*	***0.011***
Pre- training **LK** (lower case)	9.09±7.40	2.83±1.47	***0.020***	***0.008***
Pre- training **LK** (upper case)	11.73±8.92	10.67±6.71	*0.804*	*0.133*
Pre- training **LK** (total)	20.82±15.99	13.50±7.56	*0.311*	***0.038***
Post-training **LK** (lower case)	17.91±6.93	11.67±8.38	*0.119*	***0.031***
Post-training **LK** (upper case)	18.91±7.33	14.33±5.68	*0.206*	***0.012***
Post-training **LK** (total)	36.82±13.86	26.00±13.80	*0.144*	***0.018***
Socio-economic status (**SES**)	16.32±2.65	15.25±2.62	*0.438*	*0.131*
Number of books parents	4.18±1.17	3.33±1.51	*0.215*	*0.650*
Number of books child	4.55±0.93	3.50±1.22	*0.066*	*0.760*

Note: All behavioural measures have been collected before Graphogame training except for the post-training letter knowledge measures and training time.

CBCL Child Behaviour Checklist

ARHQ Adult Reading History Questionnaire

MSVT Marburger Sprachverständnistest für Kinder

BISC Bielefelder Screening zur Früherkennung von Lese-Rechtschreibschwierigkeiten

Number of books categorical measure (parents: 0=no books; 1=1-10 books; 2=11-50 books; 3=51-100 books; 4=100-200 books; 5= more than 200 books; child: 0=no books; 1=1-10 books; 2=11-20 books; 3=21-30 books; 4=31-50 books; 5= more than 50 books).

ss standard score (T = 50, SD = 10)

* Bonferroni corrected

Table 2: MNI coordinates and anatomical brain regions for fMRI activation maxima of words, symbols and the condition difference W-S (*p*<0.005, k≥29).

Region	hemisphere	MNI			T	k
		x	y	z		
Words (W)						
Cingulate gyrus	L	-6	18	48	9.38	1457
Insula	R	33	21	9	8.52	1219
Inferior occipital gyrus	L	-33	-93	-12	7.99	1335
Inferior occipital gyrus	R	36	-90	-12	7.64	1168
Insula	L	-30	18	12	6.80	947
Thalamus	R	6	-30	0	5.22	724
Symbols (S)						
Middle occipital gyrus	R	33	-93	-9	7.98	2597
Medial frontal gyrus	R	9	6	54	7.89	822
Precentral gyrus	L	-36	-12	63	6.97	2369
Inferior frontal gyrus	L	-48	3	36	6.38	162
Thalamus	R	9	-18	6	5.73	839
Inferior frontal gyrus	R	45	3	27	5.63	350
Insula	L	-42	-3	15	5.02	154
Cerebellum	R	3	-39	-27	4.82	45
Inferior frontal gyrus	R	48	36	12	4.53	59
Cingulate gyrus	R	6	-6	30	4.48	65
Cerebellum	R	0	-60	-36	4.01	41
Insula	R	36	18	9	3.82	36
Cerebellum	R	9	-57	-15	3.47	49
Condition difference (W-S)						
Medial frontal gyrus	R	15	33	33	5.05	134

Inferior frontal gyrus	L	-51	15	12	4.61	199
Middle temporal gyrus	R	51	-33	-9	4.55	130
Middle temporal gyrus	L	-54	-39	0	4.14	71
Medial frontal gyrus	L	-12	30	36	3.39	33
Note: L=left hemisphere, R=right hemisphere, MNI=Montreal Neurological Institute, k=cluster size						

Table 3: Multiple regression analyses using stepwise procedure

		B	SE B	β
Step 1	Constant	-90.04	75.65	
	Receptive vocabulary	4.89	2.61	0.47 (*)
	PAbs	1.51	2.00	0.15
	PAns	3.79	3.37	0.21
	Post-training LK	-0.04	0.47	-0.02
	RAN	-0.83	0.66	-0.24
Step 2	Constant	14.03	72.18	
	Receptive vocabulary	1.94	2.38	0.19
	PAbs	2.83	1.70	0.28
	PAns	2.90	2.76	0.16
	Post-training LK	-0.49	0.42	-0.24
	RAN	-2.28	0.75	-0.65 *
	N1 at LOT	-6.09	2.21	-0.61 *
Step 3	Constant	18.10	50.00	
	Receptive vocabulary	1.98	1.65	0.19
	PAbs	2.28	1.19	0.22 (*)
	PAns	3.92	1.93	0.22 (*)
	Post-training LK	-0.31	0.29	-0.15
	RAN	-2.66	0.53	-0.76 **
	N1 at LOT	-6.42	1.53	-0.65 **
	VWFA ROI	-64.72	17.28	-0.39 **

Receptive vocabulary, subtest of Marburger Sprachverständnistest für Kinder (MSVT); *PAbs*, phonological awareness in a broad sense*; PAns*, phonological awareness in a narrow sense*; Post-training LK*, post-training knowledge of upper and lower case letters; *RAN*, rapid naming; *LOT*, left occipito-temporal electrode cluster; *VWFS*, ROI of the condition difference with centre at MNI x=-42, y= -54, z= -17 and radius=5mm.

Average R^2=0.65 (p<0.05) for step 1; ΔR^2=.14 (p<0.05) for step 2; ΔR^2=.12 (p<0.01) for step 3
* p<0.05 ** p<0.01 (*) p<0.10

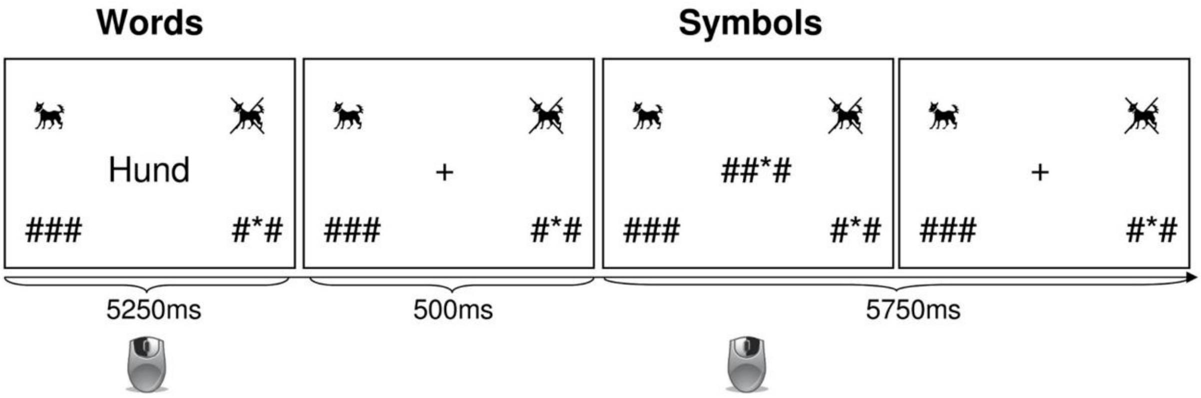
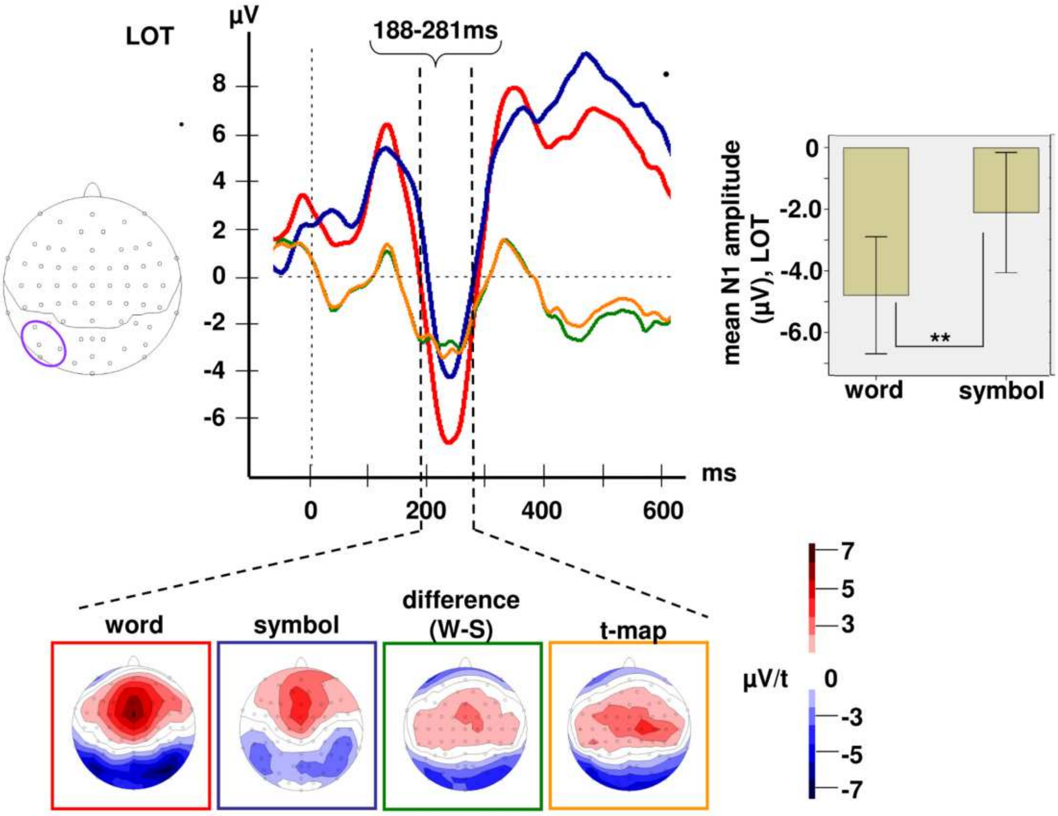
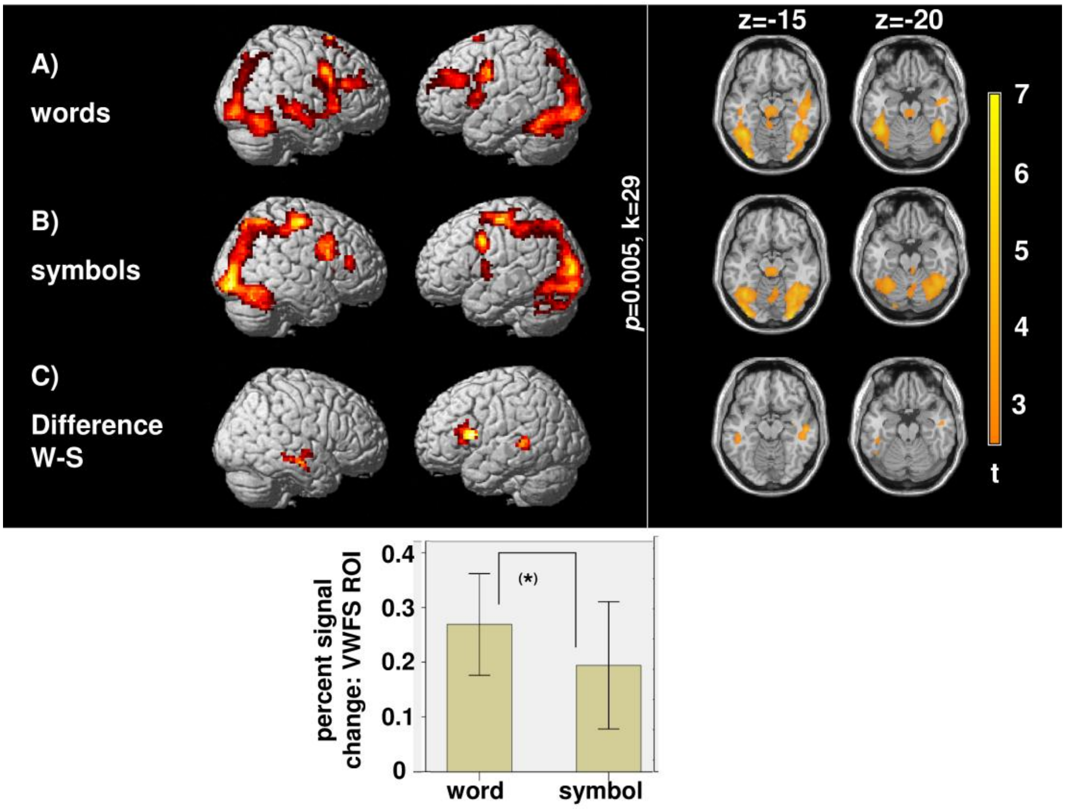


Figure 1



LOT
µV
188-281ms
8
6
4
2
0
-2
-4
-6
0
200
400
600
ms
mean N1 amplitude (µV), LOT
0
-2.0
-4.0
-6.0
**
word
symbol
word
symbol
difference (W-S)
t-map
µV/t
7
5
3
0
-3
-5
-7

Figure 2



A)
words
B)
symbols
C)
Difference
W-S
p=0.005, k=29
z=-15
z=-20
7
6
5
4
3
t
percent signal change: VWFS ROI
0.4
0.3
0.2
0.1
0
(*)
word
symbol

Figure 3

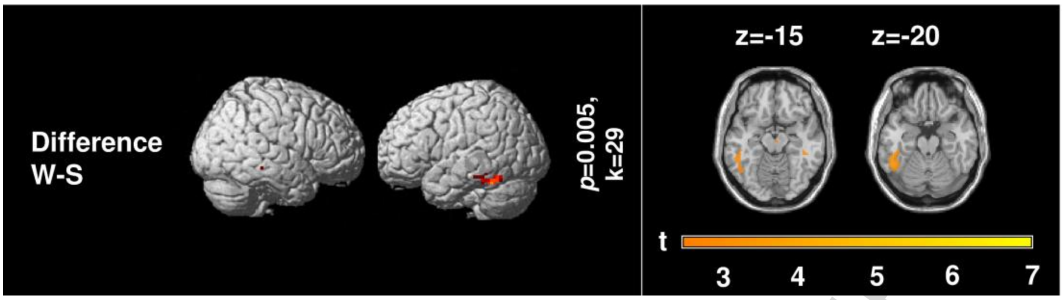


Figure 4